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ISCHAEMIC HEART DISEASE

Blocking complement to reduce perioperative risk ► To investigate whether inhibiting the pro-inflammatory effects of cytokines might decrease the risk of postoperative events, Verrier *et al* looked at the effect of a single dose of pexelizumab (a C5 complement inhibitor) on the rates of death or myocardial infarction (MI) 30 days after surgery. In those who had coronary artery bypass graft (CABG) surgery only (2732 patients), no significant difference was found in the rate of events in those receiving pexelizumab (9.8%) versus those receiving placebo (11.8%). However, in the larger population of those who received CABG and artificial valves (3099 patients), 11.5% of those receiving the drug versus 14% of those receiving placebo died or experienced MI ($p = 0.03$). This effect persisted through to day 180 of follow up. The authors propose that the reduction in events may be mediated by an amelioration of ischaemia–reperfusion injury induced inflammation via terminal complement inhibition.

▲ **Verrier ED**, Shernan SK, Taylor KM, Van de Werf F, Newman MF, Chen JC *et al*. Terminal complement blockade with pexelizumab during coronary artery bypass graft surgery requiring cardiopulmonary bypass. *JAMA* 2004;**291**:2319–27.

Statins reduce perioperative risk in non-cardiac surgery ► Approximately one million of non-cardiac operations in the USA each year are complicated by a perioperative cardiovascular event. In light of the known effects of statins on plaque stabilisation and endothelial function, this study set out to examine retrospectively the relation between statin use and postoperative mortality in non-cardiac surgery. In the 780 591 patients studied, treatment with lipid lowering agents from at least two days before surgery was associated with a lower crude in-hospital mortality (2.13% *v* 3.05%, $p < 0.001$). This relation also held true when patients were stratified according to their other risk factors for perioperative cardiac events. However, the authors acknowledge that the length of preoperative statin treatment needed to establish this advantage was not elaborated by their study.

▲ **Lindenauer PK**, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2002;**291**:2092–9.

Clopidogrel is cost effective in PVD and stroke ► Based on the lifetime treatment of a 63 year old patient facing event probabilities derived from the CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events) trial as the base case, cost effectiveness of aspirin versus clopidogrel in peripheral vascular disease (PVD), stroke, and ischaemic heart disease were calculated. Outcome measures included costs, life expectancy in quality adjusted life-years (QALYs), incremental cost effectiveness ratios, and events averted. In patients with peripheral arterial disease, clopidogrel increased life expectancy by 0.55 QALYs at an incremental cost effectiveness ratio of $25 100 per QALY, as compared with aspirin. In post-stroke patients, clopidogrel increased life expectancy by 0.17 QALYs at a cost of $31 200 per QALY. Aspirin was both less expensive and more effective than clopidogrel in post-myocardial infarction patients. In probabilistic sensitivity analyses, the evaluation for patients with peripheral vascular disease was robust. The study is limited by being a retrospective analysis of costs.

▲ **Schleinitz MD**, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. *Am J Med* 2004;**116**:797–806.

Early statin treatment for ACS ► A total of 19 537 patients with an acute coronary syndrome (ACS) were enrolled from April 1999 to September 2002. Statin use before and after presentation with ACS was associated with the composite end point including death, in-hospital MI, and stroke. Patients who were already taking statins when they presented to the hospital were less likely to have ST segment elevation (odds ratio (OR) 0.79, 95% confidence interval (CI) 0.71 to 0.88) or MI (OR 0.78, 95% CI 0.70 to 0.86). Patients who continued to take statins in the hospital were less likely to experience complications or die than patients who never received statins (OR 0.66, 95% CI 0.56 to 0.77). Patients not previously taking statins who began statin treatment in the hospital were less likely to die than patients who never received statin treatment (OR 0.38, 95% CI 0.30 to 0.48). However, adjustment for the hospital of admission attenuated the association between initiation of statin treatment and the composite end point (OR 0.84, 95% CI 0.65 to 1.10). These data support the hypothesis that statin treatment can modulate early pathophysiologic processes in patients with ACS. A randomised trial of statin treatment in acute MI is warranted.

▲ **Spencer FA**, Allegrone J, Goldberg RJ, Gore JM, Fox KAA, Granger CB, Mehta RH, Brieger D, the GRACE Investigators. Association of statin therapy with outcomes of acute coronary syndromes: the GRACE study. *Ann Intern Med* 2004;**140**:857–66.

HEART FAILURE

Not all NSAIDs increase the risk of heart failure ► Non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of congestive heart failure, but little is known about the cardiovascular effects of a newer group of NSAIDs, the cyclo-oxygenase (COX)-2 inhibitors. In this population based retrospective cohort study the investigators identified NSAID-naive individuals aged 66 years or older, who were started on rofecoxib (n = 14 583), celecoxib (n = 18 908), and non-selective NSAIDs (n = 5391), and randomly selected non-NSAID users as controls (n = 100 000). Relative to non-NSAID users, patients on rofecoxib and non-selective NSAIDS had an increased risk of admission for congestive heart failure (adjusted rate ratio (ARR) 1.8, 95% CI 1.5 to 2.2, and 1.4, 95% CI 1.0 to 1.9, respectively), but not celecoxib (ARR 1.0, 95% CI 0.8 to 1.3). Compared with celecoxib users, admission was significantly more likely in users of non-selective NSAIDs (ARR 1.4, 95% CI 1.0 to 1.9) and rofecoxib (ARR 1.8, 95% CI 1.4 to 2.4). Risk of admission for rofecoxib users was higher than that for non-selective NSAID users (ARR 1.5, 95% CI 1.1 to 2.1). Of patients with no admission in the past three years, only rofecoxib users were at increased risk of subsequent admission relative to controls (ARR 1.8, 95% CI 1.4 to 2.3).

▲ **Mamdani M**, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet* 2004;**363**:1751–56.

Defibrillators for all non-ischaemic dilated cardiomyopathy ► A total of 1520 patients who had advanced heart failure (New York Heart Association functional class III or IV) caused by ischaemic or non-ischaemic cardiomyopathies and a QRS interval of at least 120 ms were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic treatment (diuretics, angiotensin converting enzyme inhibitors, β blockers, and spironolactone) alone or in combination with cardiac resynchronisation therapy with either a pacemaker or a pacemaker-defibrillator. The primary composite end point was the time to death from or hospitalisation for any cause. As compared with optimal pharmacologic treatment alone, cardiac resynchronisation therapy with a pacemaker decreased the risk of the primary end point (hazard ratio (HR) 0.81, $p = 0.014$), as did cardiac resynchronisation therapy with a pacemaker-defibrillator (HR 0.80, $p = 0.01$). The risk of the combined end point of death from or hospitalisation for heart failure was reduced by 34% in the pacemaker group ($p < 0.002$) and by 40% in the

pacemaker-defibrillator group ($p < 0.001$ for the comparison with the pharmacologic treatment group). A pacemaker reduced the risk of the secondary end point of death from any cause by 24% ($p = 0.059$), and a pacemaker-defibrillator reduced the risk by 36% ($p = 0.003$).

▲ **Bristow MR**, Saxon LA, Boehmer J, *et al* for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.

GENERAL CARDIOLOGY

Long QTc does not predict death unless you have cardiovascular disease ▶ The seven prospective cohort studies of QTc and mortality included 36 031 individuals. There were 2677 (8.7%) individuals with prolonged QTc interval, defined as 440 ms or longer. Whereas one study reported no association between prolonged QTc interval and mortality (relative risk 1.02, 95% CI 0.70 to 1.49), the other six reported inconsistent associations overall as well as across subgroups defined by various characteristics including age, sex, and co-morbidities. In the overview, the only consistent findings were for the subgroup of patients with prior cardiovascular disease, in which relative risks ranged from 1.1 to 3.8 for total mortality, from 1.2 to 8.0 for cardiovascular mortality, and from 1.0 to 2.1 for sudden death. Further, in individuals without prior cardiovascular disease, associations were either absent or greatly attenuated; specifically, relative risks ranged from 0.9 to 1.6 for total mortality, from 1.2 to 1.7 for cardiovascular mortality, and from 1.3 to 2.4 for sudden death. In the general population, if QTc interval prolongation is associated with any increase in mortality, that risk is likely to be small and difficult to detect reliably.

▲ **Montanez A**, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH. Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. *Arch Intern Med* 2004;**164**:943–8.

When to close a PFO ▶ There is increasing interest in the association between patent foramen ovale (PFO) and documented stroke of unknown cause, commonly referred to as cryptogenic stroke. PFO is relatively common in the general population, but its prevalence is higher in patients with cryptogenic stroke. Importantly, paradoxical embolism through a PFO should be strongly considered in young patients with cryptogenic stroke. There is no consensus on the optimal management strategy, but treatment options include antiplatelet agents, warfarin sodium, percutaneous device closure, and surgical closure. High risk features in the patient's history (that is, temporal association between Valsalva inducing manoeuvres and stroke, coexisting hypercoagulable state, recurrent strokes, and PFO with large opening, large right-to-left shunt, or right-to-left shunting at rest, and a coexisting atrial septal aneurysm) should prompt PFO closure.

▲ **Wu LA**, Malouf JF, Dearani JA, Hagler DJ, Reeder GS, Petty GW, Khandheria BK. Patent foramen ovale in cryptogenic stroke: current understanding and management options. *Arch Intern Med* 2004;**164**:950–6.

Perform carotid revascularisation in asymptomatic patients with > 70% stenosis ▶ During 1993–2003, 3120 asymptomatic patients with substantial carotid narrowing on ultrasound were randomised equally between immediate carotid endarterectomy (CEA) (half got CEA by one month, 88% by one year) and indefinite deferral of any CEA (only 4% per year got CEA) and were followed for up to five years (mean 3.4 years). Kaplan-Meier analyses of five year risks are by allocated treatment. The risk of stroke or death within 30 days of CEA was 3.1% (95% CI 2.3% to 4.1%). Comparing all patients allocated immediate CEA versus all allocated deferral, but excluding such perioperative events, the five year stroke risks were 3.8% versus 11% (gain 7.2%, 95% CI 5.0% to 9.4%, $p < 0.0001$). This gain chiefly involved carotid territory ischaemic strokes (2.7% *v* 9.5%; gain 6.8%, 95% CI 4.8% to 8.8%, $p < 0.0001$), of which half were disabling or fatal (1.6% *v* 5.3%; gain 3.7%, 95% CI 2.1% to 5.2%, $p < 0.0001$), as were half the perioperative strokes. Combining the perioperative events and the non-perioperative strokes, net five year risks were 6.4% versus 11.8% for all strokes (net gain 5.4%, 95% CI 3.0% to 7.8%, $p < 0.0001$), 3.5% versus 6.1% for fatal or disabling strokes (net gain 2.5%, 95% CI 0.8% to 4.3%, $p = 0.004$), and 2.1% versus 4.2% just for fatal strokes (net gain 2.1%, 95% CI 0.6% to 3.6%, $p = 0.006$). Subgroup specific analyses found no significant heterogeneity in the perioperative hazards or (apart from the importance of cholesterol) in the long term postoperative benefits. These benefits were separately significant for males and females; for those with about 70%, 80%, and 90% carotid artery narrowing on ultrasound; and for those younger than 65 and 65–74 years of age (though not for older patients, half of whom die within five years from unrelated causes).

▲ **MRC Asymptomatic Carotid Surgery Trial Collaborative Group**. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**:1491–502.

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